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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/412,558	10/05/1999	JUALANG HWANG	08919/022001	9802

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EXAMINER	
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23

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/412,558	Applicant(s) HWANG ET AL.	
	Examiner S. Devi, Ph.D.	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,15,17,18 and 24-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,15,17,18 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☒ Interview Summary (PTO-413) Paper No(s). *19*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 09/15/03 (paper no. 20) has been entered.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendment filed 09/15/03 (paper no. 21) in response to the final Office Action mailed 06/05/02 (paper no. 10) and the Advisory Action mailed 07/08/03 (paper no. 17).

Status of Claims

3) Claims 24-27 have been amended via the amendment filed 09/15/03.

Claims 14, 15, 17, 18 and 24-27 are pending and are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Withdrawn

6) The rejection of claims 24-27 made in paragraph 11 of the office Action mailed 03/10/03 (paper no. 15) and maintained in paragraph 6 of the Office Action mailed 07/08/03 (paper no. 17) under 35 U.S.C § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendments to the claims.

7) The rejection of claims 24-27 made in paragraph 14 of the Office Action mailed 03/10/03 (paper no. 15) and maintained in paragraph 9 of the Office Action mailed 07/08/03 (paper no. 17) under 35 U.S.C. § 103(a) as being unpatentable over Hickey *et al.* (WO 97/15325 - already of record) in view of Hwang *et al.* (*J. Biol. Chem.* 264: 2379-2384, 1989 - Applicants' IDS) (Hwang *et*

al., 1989) and Pastan *et al.* (US 4,892,827 - already of record), is withdrawn in light of Applicants' amendments to the claims. A modified rejection to cover the claims, as amended, is made below.

Rejection(s) Maintained

8) The rejection of claims 14 and 18 made in paragraph 12 of the office Action mailed 03/10/03 (paper no. 15) and maintained in paragraph 7 of the Office Action mailed 07/08/03 (paper no. 17) under 35 U.S.C § 102(e) as being anticipated by Lorberboum-Galski *et al.* (US 6,140,066, filed 24 March 1998, already of record) as evidenced by Burnie *et al.* (EP 0 406 029), is maintained for reasons set forth therein and herebelow.

Applicants contend that it is well known in the art that an antigenic peptide, as recited in claim 14, contains at least one epitope and that an epitope has a stable spatial conformation so that 'it can stimulate the immune system to generate specific antibodies' that recognize the spatial conformation. Applicants point to lines 56-59 in column 2 and assert that Lorberboum-Galski *et al.* disclose a DNA sequence encoding a polypeptide including the full-length PE and 1 to 3 copies of 'flexible' linker sequence of GGGGS. Applicants submit that the linker is flexible, i.e., conformationally unstable and therefore, is not antigenic. Applicants allege that the Office has misinterpreted 'conformationally stable/unstable' as 'chemically stable/unstable'.

Applicants' arguments have been carefully considered, but are non-persuasive. Contrary to Applicants' contention, the term 'antigenic' peptide is not required, by definition, 'to stimulate the immune system to generate specific antibodies'. On the contrary, an 'immunogen' is required to stimulate the immune system to generate specific antibodies. An 'antigen' on the other hand is required to bind to a specific antibody. See section [0058] of the US 2003/0219459. Nothing in the disclosure of Lorberboum-Galski *et al.* teaches that a flexible linker sequence GGGGS is 'conformationally unstable' and is non-antigenic. Lorberboum-Galski *et al.* do not equate 'flexibility' to 'non-antigenicity' or to 'conformational instability'. Lorberboum-Galski's GGGGS peptide is not required to be 'immunogenic', but only 'antigenic' having an epitope that reacts with a specific antibody. As presented previously, Burnie *et al.* disclosed that a peptide consisting of five amino acids does serve as an 'epitope' (see last paragraph on page 3 of Burnie *et al.*). In this respect, Applicants' attention is drawn to the teachings of many in the art with regard to the spatial conformation unique to a peptide epitope. For instance, McGuinnes *et al.* (*Mol. Microbiol.* 7: 505-514, 1993) demonstrated that a peptide sequence as short as three amino acids in length, NNT,

contains an epitope (i.e., conformationally stable) that is recognized specifically by the P1.15-specific monoclonal antibody (see Table 1). The WO 93/18150 publication, already pf record, disclosed that 'an epitope can comprise 3 or more amino acids in a spatial conformation unique to the epitope, and that generally, an epitope consists of at least 5 such amino acids, and more usually, consists of at least 8-10 such amino acids' (see paragraph bridging pages 14 and 15). Granoff *et al.* (US 6,048,527) disclosed that a 'peptide epitope can comprise 3 or more amino acids in a spatial conformation unique to the epitope' (see last paragraph in column 6). It is also known in the art that many protein epitopes are conformational and are composed of discontiguous amino acid residues (see column 20, lines 55-57 of US 6,287,568). For these reasons, the prior art 5 amino acid-long peptide sequence, gly-gly-gly-gly-ser, is viewed as serving intrinsically or inherently as an antigen. The rejection stands.

9) The rejection of claims 14, 15, 17 and 18 made in paragraph 13 of the Office Action mailed 03/10/03 (paper no. 15) and maintained in paragraph 8 of the Office Action mailed 07/08/03 (paper no. 17) under 35 U.S.C § 102(b) as being anticipated by Hickey *et al.* (WO 97/15325 - already of record), is maintained for reasons set forth therein and herebelow.

Applicants contend that claims 14, 15, 17 and 18 cover nucleic acids that include a sequence encoding at least three copies of an antigenic peptide sequence. Applicants point to lines 29-32 on page 9 of Hickey's reference and state that Hickey teaches a GnRH-PE hybrid protein produced by recombinant DNA techniques that contains two tandem repeats of GnRH. Applicants submit that Hickey does not teach the use of recombinant DNA techniques to generate GnRH-PE hybrid proteins having at least three GnRH. Applicants further state that formula I at page 13 of Hickey shows a GnRH-scaffold PE conjugate that contains 2-20 GnRHs, wherein each GnRH (X) branches out from the scaffold. Applicants conclude that Hickey does not anticipate the instant claims, because Hickey's immunogenic system is a branched polymer. Applicants assert that claims 14, 15, 17 and 18 are drawn to nucleic acids that are linear polymers which encode polypeptides which are also linear polymers.

Applicants' arguments have been carefully considered, but are non-persuasive. Hickey *et al.* taught an immunogenic carrier system comprising a *Pseudomonas* exotoxin and GnRH, produced either by chemically coupling a GnRH to PE, or by recombinant DNA techniques to produce GnRH-PE hybrid proteins (see page 12, lines 8-11). Hickey's immunogenic carrier system exists with or

without the scaffold (see lines 1-5 of page 13). The PE used by Hickey *et al.* included PE variants or fragments (see page 10). A part of Hickey's paragraph bridging pages 9 and 10 states as follows:

> The preferred Pseudomonas exotoxins are variants thereof having decreased toxicity, for example, segments of Pseudomonas exotoxin wherein ... the ADP ribosylating activity has been ... inactivated through deletion .... of amino acids in the .... ribosylating domain, ...

Further, while only one immunogenic carrier system exemplified on page 9 is described as containing two GnRH molecules, the number of GnRH in the disclosed immunogenic carrier system is taught to be 2 times 1 to 10 (r), i.e., 2 through 20 GnRH. See page 13. Although one exemplified structure depicted on the upper half of page 13 appears to be a scaffolded structure, Hickey's teachings also encompass 2-20 GnRH containing non-scaffolded immunogens (see page 13, lines 1-5). Contrary to Applicants' assertion, in the first full paragraph on page 14, Hickey *et al.* explicitly taught that the scaffold is a 'linear' oligopeptide. Therefore, more than two linear GnRH molecules are not excluded from the Hickey's linear immunogenic carrier system, i.e., GnRH-PE chimeric hybrid proteins produced by using recombinant DNA technology. Hickey's hybrid proteins contain contiguous sequences of the constituent proteins or peptides encoded by recombinant DNA sequences (see pages 20, 29 and 30). The rejection of claims 14, 15, 17 and 18 as being anticipated by Hickey *et al.* stands.

Rejection(s) under 35 U.S.C § 101

10) 35 U.S.C. § 101 states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this cycle.

11) Claims 14, 15, 17, 18 and 24-27 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

Instant claims, as written, do not sufficiently distinguish over nucleic acids as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty, 447 U.S. 303, 206 USPQ 193 (1980)*. The claim(s) should be amended to indicate the hand of the inventor, e.g., by insertion of 'An isolated" as described in page 10 of specification. See MPEP 2105.

Rejection(s) under 35 U.S.C § 102

12) Claim 24 is rejected under 35 U.S.C. § 102(b) as being anticipated by Gray *et al.* (*PNAS* 81: 2645-2649, 1984) as evidenced by Covacci *et al.* (WO 93/18150 - already of record).

The transitional limitation "comprises" similar to the limitations such as, "has", "includes," "contains," or "characterized by," represents open-ended claim language and therefore does not exclude additional, unrecited elements. See M.P.E.P 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). On the other hand, the limitation "consisting of" represents closed claim language and excludes any element, step, or ingredient not specified in the claim. *In re Gray, 53 F.2d 520, 11 USPQ 255 (CCPA 1931)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)*.

Gray *et al.* taught an isolated *Pseudomonas* DNA which encodes an exotoxin A polypeptide wherein the polypeptide comprises: (a) a *Pseudomonas* exotoxin A fragment consisting of the receptor binding domain, i.e., 1-252 amino acid residues of *Pseudomonas* exotoxin A; and (b) at least two copies an antigenic peptide sequence, ala ala gly glu, one at positions 375-378 and another at positions 523-526 of the polypeptide. See Figure 1; Materials and Methods; and Results. That the prior art *Pseudomonas* exotoxin A represents a polypeptide that 'comprises' a *Pseudomonas* exotoxin A fragment consisting of the receptor binding domain of *Pseudomonas* exotoxin A is inherent from the teachings of Gray *et al.* That the prior art 4 amino acid-long peptide sequences, ala-ala-gly-glu, serve as antigenic peptides is inherent from the teachings of Gray *et al.* in light of what is well known in the art. For instance, Covacci *et al.* disclosed that a peptide comprising three amino acids will have the spatial conformation unique to an epitope or antigenic determinant (see paragraph bridging pages 14 and 15 of Covacci *et al.*).

Claim 24 is anticipated by Gray *et al.* Covacci *et al.* is **not** used as a secondary reference in combination with Gray *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Gray *et al.* See *In re Samour* 197 USPQ 1 (CCPA 1978).

13) Claim 14 is rejected under 35 U.S.C. § 102(b) as being anticipated by Gray *et al.* (*PNAS* 81: 2645-2649, 1984) as evidenced by Covacci *et al.* (WO 93/18150 - already of record).

The transitional limitation "comprises" similar to the limitations such as, "has", "includes,"

"contains," or "characterized by," represents open-ended claim language and therefore does not exclude additional, unrecited elements. See M.P.E.P 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). On the other hand, the limitation "consisting of" represents closed claim language and excludes any element, step, or ingredient not specified in the claim. *In re Gray, 53 F.2d 520, 11 USPQ 255 (CCPA 1931)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)*.

Gray *et al.* taught an isolated *Pseudomonas* DNA which encodes an exotoxin A polypeptide wherein the polypeptide comprises: (a) the receptor binding domain, i.e., 1-252 amino acid residues of *Pseudomonas* exotoxin A; and (b) at least three copies an antigenic peptide sequence, gly asp, one at positions 322-324; another at positions 404-406; and the third peptide at positions 579-581 of the polypeptide. See Figure 1; Materials and Methods; and Results. That the prior art *Pseudomonas* exotoxin A represents a polypeptide that 'comprises' the receptor binding domain of *Pseudomonas* exotoxin A is inherent from the teachings of Gray *et al.* That the prior art 3 amino acid-long peptide sequences, gly-gly-asp, serve as antigenic peptides is inherent from the teachings of Gray *et al.* in light of what is well known in the art. For instance, Covacci *et al.* disclosed that a peptide comprising three amino acids will have the spatial conformation unique to an epitope or antigenic determinant (see paragraph bridging pages 14 and 15 of Covacci *et al.*).

Claim 14 is anticipated by Gray *et al.* Covacci *et al.* is **not** used as a secondary reference in combination with Gray *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Gray *et al.* See *In re Samour* 197 USPQ 1 (CCPA 1978).

Rejection(s) under 35 U.S.C. § 103

14) Claims 14, 15, 17 and 18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hickey *et al.* (WO 97/15325 - already of record) in view of Russell-Jones *et al.* (WO 91/02799 - already of record).

The transitional limitation "comprises" similar to the limitations such as, "has", "includes," "contains," or "characterized by," represents open-ended claim language and therefore does not

exclude additional, unrecited elements. See M.P.E.P 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). On the other hand, the limitation "consisting of" represents closed claim language and excludes any element, step, or ingredient not specified in the claim. *In re Gray, 53 F.2d 520, 11 USPQ 255 (CCPA 1931)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)*.

Hickey *et al.* taught GnRH-PE chimeric hybrid proteins produced by recombinant DNA technology (see third full paragraph on page 6; second full paragraph on page 7; page 12, third full paragraph; and last paragraph on page 10). The recombinant DNA encoding the hybrid proteins of the invention are taught on pages 20, 21, 29 and 30. The GnRH peptide has the amino acid sequence of SEQ ID NO: 1 (see second full paragraph on page 8). The hybrid proteins contain contiguous sequences of the constituent proteins/peptides and are preferably manufactured through expression of recombinant DNA sequences (see page 29, second full paragraph). One example of a GnRH-PE chimeric hybrid protein contains two tandem repeats of GnRH (see page 9). The hybrid GnRH protein manufactured can comprise as many as 2 to 20 native GnRH molecules (see page 13). Hickey *et al.* taught that a variant of *Pseudomonas* exotoxin can also be used in the hybrid construct (see page 7; and claims). The preferred *Pseudomonas* exotoxin (PE) used in the hybrid protein is a PE variant or fragment having decreased toxicity, i.e., a segment of PE wherein the ADP ribosylating activity has been deleted, i.e., a fragment of PE which retains the receptor binding domain of PE. Hickey *et al.* expressly taught that the efficacy of PE as an immunogenic carrier protein is independent of the toxin activity of the PE (see last full paragraph on page 9; and the paragraph bridging pages 9 and 10). Thus, Hickey *et al.* taught the decreased toxicity of the PE variant or fragment having the ADP ribosylating segment deleted, i.e., a fragment of PE which retains the receptor binding domain of PE. Hickey *et al.* disclosed conjugates of GnRH-PE containing 2 to 20 contiguous molecules of GnRH (see pages 13, 17, 20 and 29). That the prior art PE having the ADP ribosylating segment deleted serves as the receptor binding domain is inherent from the teachings of Hickey *et al.* who identified the portion of PE containing 1-252 amino acids to be the binding region (see paragraph bridging pages 9 and 10).

If one viewed Hickey *et al.* as not expressly teaching a nucleic acid encoding a polypeptide comprising the receptor binding domain of a *Pseudomonas* exotoxin A and at least three copies or 10-20 of an antigenic peptide sequence, such as, GnRH (SEQ ID NO: 1), then the instant claims would have been obvious over Hickey *et al.* for the following reasons.

Russell-Jones *et al.* expressly taught recombinant polynucleotide molecules encoding LHRH fusion proteins (see abstract; and page 7, last two paragraphs). Russell-Jones *et al.* taught that insertion of tandem repeats of LHRH analogues (i.e., peptide sequences including SEQ ID NO 1) gives more immunogenic fusion than the insertion of a single insert (see page 6, lines 26-29). Russell-Jones *et al.* expressly taught the use in fusion constructs of four and eight LHRH analogue inserts (see page 29, lines 4-6; page 21, lines 1-7; and Figure 5). Russell-Jones *et al.* explicitly taught that multiple inserts of LHRH analogue were consistently more immunogenic in evoking a higher anti-LHRH response than constructs containing a single insert (see page 29, lines 26-29). Russell-Jones *et al.* demonstrated that an increase in LHRH antibody levels in dogs corresponded to an increase in the LHRH analogue units in the fusion protein construct and concluded that the introduction of multiple copies of the peptide in the fusion construct considerably enhances the immunogenicity of the inserted peptide (see page 30, lines 4-10).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to increase the number of GnRH repeats in Hickey recombinant DNA fusion construct to three or 10-20 to produce the instant invention, with a reasonable expectation of success, because Russell-Jones *et al.* expressly taught the use of multiple inserts of LHRH in the recombinant fusion construct renders it more immunogenic and evokes higher anti-LHRH response. One of skill in the art would have been motivated to introduce multiple copies of upto 20 GnRH in Hickey's construct for the expected benefit of considerably enhancing the immunogenicity of Hickey's GnRH peptide as taught by Russell-Jones *et al.*

Claims 14, 15, 17 and 18 are *prima facie* obvious over the prior art of record.

15) Claims 24-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hickey *et al.* (WO 97/15325 - already of record) in view of Hwang *et al.* (*J. Biol. Chem.* 264: 2379-2384, 1989 - Applicants' IDS) (Hwang *et al.*, 1989) or Hwang *et al.* (US 6,387,684) ('684) and Pastan *et al.* (US 4,892,827 - already of record).

The reference of Hwang *et al.* ('684) is used in this rejection since it qualifies as prior art under 35 U.S.C. § 102(e) and accordingly is not disqualified as art under 35 U.S.C. § 103(a).

The teachings of Hickey *et al.* are explained above. If one viewed Hickey *et al.* as not expressly teaching a nucleic acid encoding a polypeptide comprising *Pseudomonas* exotoxin A polypeptide consisting of the receptor binding domain of *Pseudomonas* exotoxin A and at least two copies, or 10-20 copies of an antigenic peptide sequence, such as, GnRH (SEQ ID NO: 1), then the instant claims would have been obvious over Hickey *et al.* for the following reasons.

The use of *Pseudomonas* exotoxin consisting of the receptor binding domain Ia for vaccination or *in vivo* administration was taught or suggested in the art. For example, Hwang *et al.* (1989) taught a nucleic acid sequence encoding domain Ia of PE. Hwang *et al.* (1989) expressly taught that domain Ia of PE can be used for vaccination purposes (see right column on page 2379).

Similarly, Hwang *et al.* ('684) disclosed the use of a fusion polypeptide comprising a *Pseudomonas* exotoxin A fragment consisting of domain Ia for *in vivo* delivery of biomolecules (see third full paragraph in column 2; and claim 2). Hwang *et al.* ('684) disclosed a polypeptide consisting of a receptor binding domain of a *Pseudomonas* exotoxin A said domain being SEQ ID NO. 5 consisting of amino acid residues 1-252 of *Pseudomonas* exotoxin A. See claims; and columns 11 and 12. Thus, both Hwang *et al.* (1989) and Hwang *et al.* ('684) taught the suitability of domain Ia of PE alone for *in vivo* administration. One of skill in the art would understand that Hwang's (1989 or '684) domain Ia of PE serves as a variant of *Pseudomonas* exotoxin.

Similarly, Pastan *et al.* taught recombinant gene fusions using PE (see column 6, lines 30 and 31) and the pJH14 plasmid that encodes structural domain Ia of PE comprising amino acids 1-252 (see column 6, lines 60 and 61). Pastan *et al.* expressly taught the fusion of PE or part of PE with other polypeptides, including luteinizing hormone (see column 6, lines 36-43). Pastan *et al.* specifically taught that the protein encoded by domain I could be administered for treatment purpose, because it would block toxin binding to cells (see column 1, lines 15-18).

Given the express teaching of Hwang *et al.* (1989 or '684) that domain Ia of PE can be used for vaccination or *in vivo* delivery purposes, and Hickey's explicit teaching that a variant of PE with the ADP ribosylating segment deleted, is preferably used in their GnRH-PE chimeric hybrid protein construct, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the

invention was made to specifically use Hwang's nucleic acid sequence encoding only domain Ia of PE, in Hickey's fusion construct in place of the nucleic acid encoding whole PE, to produce the nucleic acid of the instant invention, with a reasonable expectation of success, because Pastan *et al.* expressly taught that fusion can be performed with luteinizing hormone and a part of PE, and Hickey *et al.* expressly taught a variant of PE with the ADP ribosylating segment deleted and having decreased toxicity as a preferred PE variant in their GnRH-PE chimeric hybrid protein construct. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of blocking the toxin binding to cells as taught by Pastan *et al.* and for providing a PE variant that has diminished toxicity as taught by Hickey *et al.*

Claims 24-27 are *prima facie* obvious over the prior art of record.

Remarks

16) Claims 14, 15, 17, 18 and 24-27 stand rejected.

17) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center receives transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

18) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached at (703) 308-3909.

S. DEVI, PH.D.
PRIMARY EXAMINER

December, 2003